UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUL - 6 1989

Dr. Elaine Dorwood-King
Monsanto Company
1101 17th Street NW.
Washington, DC 20036

Dear Dr. Dorwood-King:

Subject: MON 0139 (Additional Information For
Mouse Oncogenicity Study)
EPA Registration No. 524-318
MON 0139 62% Solution
EPA Registration No. 524-333
Your Letter Dated December 12, 1988

The scientific review and evaluation of the information submitted above have been completed. The following are our conclusions/comments.

1. The historical control data show that the incidence of renal neoplasms in male CD-1 mice ranged from 0 to 3.3 percent at Biodynamics (laboratory that performed the glyphosate mouse oncogenicity study), 0 to 4.7 percent at Hazelton, 0 to 1.7 percent at IRDC, 0 to 3.3 percent at Litton Bionetics, and 0 to 1.4 percent in Japan (Japanese Institute for Environmental Toxicology).

2. The range of incidences of 0 to 7.1 percent reported in the November 10, 1988 meeting with the Agency was taken from the data on F_1 male mice in reproduction studies at Hazleton. These F_1 data could not be further substantiated by Monsanto and, therefore, cannot be used to support the Monsanto position.

3. Other data (two chronic bioassays wth male CD-1 mice) submitted are not convincing.

4. A repeat of the mouse oncogenicity will not be required at this time. After the results of the new 2-year rat chronic toxicity and oncogenicity study are reviewed, the Agency will reconsider if a repeat mouse oncogenicity study is needed.

Sincerely yours,

Robert J. Taylor
Product Manager (25)
Fungicide-Herbicide Branch
Registration Division (H7505C)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Company copy

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JUN 19 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate - EPA Registration Nos. 524-318 and 524-333 - Historical Control Data for Mouse Kidney Tumors

MRID No.: 00130406
Caswell No.: 661A
Record No.: 238,412
Project No.: 9-0697

FROM: William Dykstra, Reviewer
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

William Dykstra 6/9/89

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Edwin Budd, Acting Branch Chief
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

and

William Burnham, Deputy Director
Health Effects Division (H7509C)

Requested Action

Review historical control data on mouse kidney tumors submitted by Monsanto in response to meeting of November 10, 1988.

Conclusions and Recommendations

The historical control data showed that the incidence of renal neoplasms in male CD-1 mice ranged from 0 to 3.3 percent at Bio/dynamics (the laboratory that performed the glyphosate mouse oncogenicity study), 0 to 4.7 percent at Hazleton, 0 to 1.7 percent at IRDC, 0 to 3.3 percent at Litton Bionetics, and 0 to 1.4 percent in Japan (Japanese Institute for Environmental Toxicology). The range of incidences of 0 to 7.1 percent reported by Monsanto in their November 10, 1988 meeting with the Agency was taken from the data on F_1 male mice in reproduction studies at Hazleton.

These F_1 data could not be further substantiated by Monsanto and therefore, cannot be used to support the Monsanto position.

Other data study presented by Monsanto, briefly, were two chronic bioassays with male CD-1 mice in which the following incidences of renal neoplasms were noted:

	Control	Low	Mid	High
Study I	0/80	2/80	1/80	2/80
Study II	2/50	1/50	3/50	3/50

Monsanto cites these data as showing an incidence of 0 to 6 percent in control or treated groups (the occurrences of renal tumors in treated groups were not considered compound-related) which matches the upper incidence of 6 percent in the glyphosate study. Toxicology Branch (TB) does not consider these random data as convincing.

However, based on a meeting held June 7, 1989 between W. Dykstra, E. Budd, and W. Burnam, TB concludes that a repeat of the mouse oncogenicity study is not required at this time. After the results of the new 2-year rat chronic toxicity and oncogenicity study are reviewed, TB will reconsider whether the repeat of the mouse oncogenicity study is required.

Background

On November 10, 1988, a meeting was held between EPA staff and representatives of Monsanto to discuss the Agency's requirement that the mouse oncogenicity study with glyphosate be repeated (memorandum attached).

Monsanto stated that there were historical control data demonstrating that the incidence of mouse kidney neoplasms ranged from 0 to 7.1 percent. This incidence exceeded the incidence of 6 percent from the high-dose group in the glyphosate study. Monsanto indicated that a repeat mouse oncogenicity study was not required.

EPA stated that the historical control data should be submitted in order to reevaluate the Agency's position on the repeat study.

In response to this request, Monsanto has submitted historical control data from several sources to substantiate their contention regarding the range of mouse kidney tumor neoplasms.

Review

1. The incidence of renal tubule tumors in the glyphosate mouse study is shown below:

	Mouse Kidney			
Dose (ppm)	0	1000	5000	30,000
No. Examined	49	49	50	50
Tubular Adenomas	1	0	1	3
Percent Incidence	2%	0%	2%	6%

2. The historical control data are presented below and are also attached to this memorandum.

   a. Bio/dynamics Historical Control Data - From studies initiated between 1976 and 1980 and terminated between 1978 and 1982, the incidence of tumors is shown below as submitted by Monsanto:

CD-1 COBS (ICR Derived) Mice
Bio/dynamics, Inc.
MALES - KIDNEYS

CONTROL DATA

STUDY I.D.	A	B	C	D	E	F	G	H*	I	J**	K+	L	M**	N	O	P
Tissue/Finding																
No. Examined	111	121	104	119	120	120	120	15	50		47	49		200	50	60
NEOPLASTIC FINDINGS																
B-Tubular Adenoma	1				2											
M-Tubular Carcinoma																

B = benign; M = malignant.
Control groups IA and IB counted together.
+ Study K = common control animals used for two test articles.
* = Gross Lesions only - kidney not routinely examined.
** = No microscopic findings recorded to date.

Note: Search for Renal Tubular Carcinomas revealed no incidence in these studies.

Male Charles River CD-1 Mice
Bio/dynamics, Inc.
KIDNEY

CONTROL DATA

STUDY I.D.	A		B		C		D		E		F		G	
	*	**	*	**	*	**	*	**	*	**	*	**	*	**
Tissue/Finding														
Neoplasm No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
B - Tubular Adenoma		01								02				

*Control Group A	Start	6/78	12/77	12/77	10/78	11/78	11/77	10/77
**Control Group B	Terminate	7/80	4/80	3/80	4/81	4/81	4/80	4/80

Discussion

It can be seen from the above data that the range of historical controls of mouse renal neoplasms from Bio/dynamics is 0 to 3.3 percent. It should be noted that the glyphosate mouse oncogenicity study was conducted by Bio/dynamics between 1980 and 1982. Therefore, the 6 percent incidence of renal tumors in the high-dose group in the glyphosate mouse study exceeds the upper limit of the range of 3.3 percent in the historical

b. Hazleton's Historical Control Data

In a letter dated December 2, 1988 from J.M. Burns of Hazleton to D. Ward of Monsanto, six studies are cited as shown below:

The incidences are for scheduled sacrifices and unscheduled deaths combined.

Study	Type	Init.	Term.	Tubular Cell Carcinoma, Males
1	Dietary	3/80	3/82	2/43
2	Dietary	4/80	4/82	1/100
3	Dietary	9/81	9/83	0/80
4	Dietary	12/79	12/81	0/50
5	Dietary	5/82	5/84	0/60
6	Gavage	8/83	8/85	0/47

Tubular cell carcinomas only were observed.

Discussion

The range of mouse renal neoplasma cited by Hazleton is 0 to 4.7 percent. Therefore, the incidence of 6 percent in the high-dose group of the glyphosate mouse study exceeds the historical controls from Hazleton.

Additional, Monsanto has submitted "representative historical control data" from Hazleton reproduction studies in which renal neoplasia occurred in groups of F_1 generation control mice which were sacrificed after 91 to 105 weeks. These data are shown below:

NEOPLASIA IN CD-1® F_1 MICE - UNTREATED CONTROLS

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)
TISSUE NAME--KIDNEY		
TUBULAR CELL ADENOMA		
	1	15
	1	14
POSITIVE TOTALS	2	29
OVERALL TOTALS	2	56
OVERALL PERCENT	3.6	
RANGE OF PERCENTAGES	7	7
TUBULAR CELL CARCINOMA		
	1	15
POSITIVE TOTALS	1	15
OVERALL TOTALS	1	56
OVERALL PERCENT	1.8	
RANGE OF PERCENTAGES	7	7

Discussion

Apparently, this historical control data, which range from 0 to 7.1 percent, are the historical control data cited by Monsanto in their meeting with EPA on November 10, 1988. In a telephone communication on January 30, 1989 to Dr. Ward of Monsanto (314-694-8818), Dr. Ward indicated that Hazleton was unable to provide any additional details (dates of study, supplier, pathologists, etc.) about these particular historical controls. Therefore, in light of this telephone communication, TB concludes that these particular historical controls from F_1 male mice cannot be used to substantiate the Monsanto position.

C. IRDC Historical Control Data

Historical control data from IRDC on the incidences of renal neoplasms in CD-1 male mice in 19 studies of 24 to 25 month duration conducted between 1976 and 1978 are summarized below.

Tumors	No. Tumors	Range	No. Examined
Kidneys			1490
Adenoma	3	0-1.3	
Carcinoma	4	0-1.7	

Discussion

The range of 0 to 1.7 percent for renal neoplasms at IRDC does not exceed the incidence of 6 percent in the high-dose group of the glyphosate mouse study. The submitted historical control data from IRDC did not show the individual study incidences and therefore, is limited in this respect.

D. Spontaneous Renal Neoplasms Observed on 18 Food Color Additive Studies

Monsanto has submitted the incidence of renal neoplasms from 18 food color additive chronic studies with CD-1 mice (supplied to Monsanto by Dr. J.K. Haseman of NIEHS). These data are presented below:

INCIDENCE OF RENAL NEOPLASMS IN CONTROL MALE CD-1 MICE

Study ID[a]	Testing[b] Laboratory	Lesion Description	Incidence Group A	Group B
Blue No. 1	IRD	Cortical adenoma	0/60	1/60
Blue No. 2	B/d	Tubular cell adenoma	0/57	1/54
Green No. 3	B/d		0/51	0/53
Green No. 5	HL	Tubular cell adenoma	1/59	0/59
Yellow No. 5	IRD		0/60	0/60

a/A series of chronic bioassays in Charles River CD-1 mice were conducted on 18 food color additives. These studies were sponsored by the Certified Colors Manufacturers Association; the Cosmetic, Toiletries, and Fragrance Association; and the Pharmaceutical Manufacturers Association. Each study utilized 2 concurrent control groups of 60 mice/sex/group. These studies were conducted during the period of 1977 to 1980.

b/Testing laboratories were: International Research and Development Corporation (IRD); Bio/dynamics, Inc. (B/d); Hazleton Laboratories (HL); and Litton Bionetics (LB).

INCIDENCE OF RENTAL NEOPLASMS IN CONTROL MALE CD-1 MICE (Cont'd)

Study ID	Testing Laboratory	Lesion Description	Incidence Group A	Incidence Group B
Yellow No. 6	B/d		0/61	0/60
Yellow No. 10	B/d		0/60	0/60
Orange No. 5	B/d		0/60	0/60
Orange No. 17	B/d	Tubular cell adenoma	0/60	2/60
Red No. 3	IRD		0/60	0/60
Red No. 6	IRD		0/60	0/60
Red No. 9	LB	Tubular cell adenoma	0/59	2/60
Red No. 9		Tubular cell adenocarcinoma	1/59	0/60
		Cholesterol granuloma	1/59	0/60
Red No. 19	B/d		0/54	0/57
Red No. 21	IRD	Adenoma (N.O.S.)	1/60	0/60
Red No. 27	LB	Tubular cell adenoma	1/60	0/59
		Hemagiosarcoma	1/60	0/59
Red No. 30	HL		0/60	0/58
Red No. 33	IRD	Tubular cell adenoma	1/60	0/60
		Cortical carcinoma	1/60	0/60
Red No. 36	LB		0/60	0/60

Discussion

The incidence of renal tubular neoplasms ranged from 0 to 3.3 percent. It should be noted that the 3.3 percent incidence (2/60) of tubular cell adenoma in Orange No. 17 from Bio/dynamics was previously reported by Monsanto as historical

control data by Bio/dynamics and does not represent additional findings. The incidence of 3.3 percent (2/60) for renal tubular cell adenoma in Red No. 9 from Litton Bionetics was not previously reported and is considered new data.

E. Historical Control Data in CD-1 Mice From The Institute of Environmental Toxicology (Tokyo, Japan).

The incidence of renal neoplasms from male CD-1 mice was 6/891 (0.67%). In a telephone communication on January 30, 1989 with Dr. Ward of Monsanto, Dr. Ward indicated that for individual studies the incidence of renal neoplasms ranged from 0 to 1.4 percent (1/70). The range of 0 to 1.4 percent of renal neoplasms is comparable to the incidences observed at other laboratories.

Attachments

WHY THE GLYPHOSATE MOUSE ONCOGENCITY STUDY IS NOT REQUIRED

The Agency requests a repeat of the chronic feeding/oncogenicity study in mice to fully address the questions of "... whether the apparent effects noted in the mouse study [renal tubular adenomas] are biologically relevant." The results of the mouse bioassay do not provide positive, or even suggestive, evidence of carcinogenicity. The most that can be said is that the results were equivocal as, in fact, the Scientific Advisory Panel stated. Furthermore, the SAP pointed out the fact that this equivocal finding occurred only at a dose level that exceeded the MTD. Quoting from the SAP report, "... no oncogenic effect is demonstrated using concurrent controls" and"... the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls." There appears to be no justification for requiring the repeat of a study with equivocal findings at a single site, only at dosage levels exceeding the MTD.

Several expert toxicologists intimately familiar with the glyphosate chronic/oncogenic mouse study results, and personally involved in the SAP hearing on this issue, were asked to evaluate the need for a repeat study. All experts agreed that additional testing is not justified since the current study was conducted at levels exceeding the MTD and failed to demonstrate a treatment-related oncogenic effect. Their evaluations are enclosed in this part.

As discussed previously, the fact that Monsanto has agreed to repeat the chronic/oncogenic rat study with glyphosate diminishes even further the justification for a repeat mouse study. As pointed out by Dr. Farber at the SAP hearing, "If in fact there wasn't a remaining MTD issue in regard to the rat study, and the rat was run at a somewhat higher level and nothing was seen, then basically the whole thing comes out as no evidence of carcinogenicity." The results of the current rat and mouse studies, along with results to be obtained from a repeat rat study, should be sufficient to assess the oncogenic potential of glyphosate. A repeat mouse study is not necessary.

Finally, based upon a review of the principles expressed in the Agency's draft "Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies", it is clear that the chronic/oncogenic mouse study was conducted at dosage levels which greatly exceeded the upper limit of 7,000 ppm required for mouse studies. Furthermore, none of the requirements listed in that document which would necessitate a study are fulfilled for the mouse study (see Attachment 1).

Statement of Robert A. Squire
Concerning a Possible Repeat of
The Glyphosate Bioassay in Mice

Repeat of a chronic animal bioassay can be justified on the basis of several deficiencies but none of them are present in the case of glyphosate. The maximum tolerated dose was met or exceeded in a well validated study, and there was no biologically or statistically significant increase in tumors.

All pathologists who examined the mouse kidney slides and data expressed the view that the renal adenomas in male mice could not be attributed to the test compound. It is difficult to see a basis on which a study can be considered positive or even suggestive if there is no statistically significant increase in tumors and the scientists directly involved find no biological evidence of a compound-related tumorigenic effect. As I indicated in my letter of September 29, 1986, the weight of evidence including the absence of preneoplastic lesions in addition to the 3 adenomas in high-dose males strongly suggest that the tumors were naturally occurring. This view was shared by Dr. Marvin Kuschner and the original pathologists.

Attachment A from The Environmental Protection Agency document entitled "Guidance for the Regulation of Pesticide Products Containing Glyphosate" states on page 6 that "Glyphosate produced

an equivocal oncogenic response in the mouse, causing a slight increase in the incidence of renal tubular adenomas .... ". There is clearly a presumption by EPA that the tumors were compound-related. By definition, such a presumption cannot be supported by equivocal data, and it was not supported by the Scientific Advisory Panel findings. As stated in their Report, ".... no oncogenic effect is demonstrated using concurrent controls", and ".... the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls".

The most severe judgement applied to the study by the SAP was also that the finding was "equivocal". Equivocal data are frequent in chronic bioassays in the National Toxicology Program and elsewhere. Unless such a finding occurs in a study that failed to administer an MTD, it does not provide a basis for retesting. Where only equivocal findings result, even after long-term exposure to maximum tolerated doses, it is difficult to believe that a carcinogenic effect may have been "missed". Or if such an effect was missed, that it could be demonstrated by retesting within any reasonable experimental design limits. If our years of animal testing experience have taught us anything, it is that such tests are relatively imperfect assays and that retesting rarely resolves initial disputes. Furthermore, to require retesting in cases of equivocal findings would, I fear, set a precedent that would overwhelm toxicology resources and produce endless delays in chemical testing.

In summary, the weight of evidence indicates that no tumorigenic effect was evident in mice chronically exposed to glyphosate at a maximum tolerated dose. There is no reason to believe that retesting would produce a different result.

Robert A. Lewis

October 8, 1986

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OCT 16 1986

PATHCO INC.
P O Box 2489 Gaithersburg, MD 20879 (301) 831-8518

October 14, 1986

Dr. Timothy J. Long
Senior Product Toxicologist
Monsanto Agricultural Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167

Dear Tim:

You asked me to comment on EPA's request that Monsanto repeat the mouse oncogenicity study for Glyphosate because of what EPA terms the equivocal finding of renal tumors in the kidneys of male mice. As you know, I do not believe these neoplasms are related to administration of Glyphosate and so feel the current test is adequate.

However, assuming there is some question regarding the significance of these lesions, I feel a retest under the same conditions would not add any new information. Two ways to increase the sensitivity of a carcinogenicity test are 1) to increase the number of animals and/or 2) to increase the dose. The EPA has suggested that the number of animals/group be increased in order to increase the statistical power of the study. It seems to me that in order to prove conclusively statistically that these neoplasms are or are not related to Glyphosate would require a "megamouse" study. The cost for such a study would be extremely expensive. With regard to increasing the dose in a new study, based on the data from the subchronic and chronic mouse studies, I think a higher dose would likely compromise the study. In fact, there is concern that the dose already tested (30,000 ppm or 3% of the diet) was too high. The EPA has proposed, in a "Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies", that the maximum dose in a mouse oncogenicity study should be 7,000 ppm (0.7% of the diet). Thus, the highest dose in the Glyphosate chronic mouse study far exceeds EPA recommendations. If the EPA recommendations for the high dose, i.e. 7,000 ppm, had been followed, it is possible that even at 30,000 ppm the mild toxic changes observed would not have been observed. Indeed, at 5000 ppm no toxic effects were observed.

In the same position paper, EPA presents a decision tier scheme for determining whether a chronic study needs to be repeated. Based on this scheme, there does not appear to be

any reason to repeat the mouse oncogenicity study for Glyphosate. The only possible areas of concern would be those related to an oncogenicity study in a second species. I understand that Monsanto is intending to repeat the rat oncogenicity study and, therefore, it would seem that these areas will be addressed.

Based on EPA's guidelines, it appears that they have adequate information from the current mouse oncogenicity study to adequately assess potential human risk and that a repeat of this study would be for academic curiosity.

Sincerely,

Dawn G. Goodman, V.M.D.
Diplomate, ACVP

DGG/ma

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Agency's Proposed Action on the Non-Wood Uses of Pentachlorophenol as Set Forth in the Position Document 4

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) decision to cancel most of the non-wood uses of Pentachlorophenol and modify the terms and conditions for registration of the remaining uses. The review was conducted in an open meeting held in Arlington, Virginia, on February 11, 1986. All Panel members were present for the review.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency and from Mr. David H. Fussell, Mr. Maurice Jones, Dr. Kenneth J. Macek, and Mr. Robert T. Seith for the Chapman Chemical Company.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

Pentachlorophenol

The Agency requested the Panel to focus its attention upon a set of issues relating to the pesticide Pentachlorophenol. There follows a list of the issues and the SAP's response to the questions.

1. The Panel is specifically requested to comment on the Agency's assessment of the ecotoxicological hazard of Pentachlorophenol to aquatic organisms.

2. The Panel is specifically requested to comment on the Agency's assessment of risk to aquatic organisms from the use of Pentachlorophenol in pulp and paper mills and in oil well water operations.

Panel Response:

The Panel found the data and data analysis presented in the Draft PD 4 and related documents to be inadequate for a thorough scientific review of the ecotoxicological risk presented by the uses of Pentachlorophenol (PCP) in pulp and paper mills and in oil well operations. The Panel, however, concurs with the Agency's assessment of PCP's toxicity for aquatic biota, and is concerned about the potential hazards to ecological and human health from the non-wood uses of PCP. Thus, we recommend a reanalysis of risk and a thorough rewrite of the PD 4 document, followed by a resubmission of this material to the SAP.

The reanalysis and rewrite should take into account the following:

(1) the most recent data obtainable on PCP uses,

(2) a reevaluation of trace dibenzodioxin and dibenzofuran contamination in PCP products formulated for non-wood uses,

(3) a reevaluation of potential exposure to aquatic biota from pulp and paper and oil field uses,

(4) a reanalysis of ecotoxicological risk based on extant toxicity data and the reevaluated exposure analysis,

(5) a more complete analysis of the availability and comparative risk of alternatives to replace current non-wood uses of PCP, and

(6) a presentation of both upper and lower bounds for risk estimates to applicators (pp. 21-22).

The Panel also recommends an evaluation of potential human exposure to PCP (and trace technical grade contaminants) through other non-wood uses.

To obtain adequate information it may be necessary for the Agency to issue a data call-in from registrants holding non-wood use registrations.

FOR THE CHAIRMAN

Certified as an accurate report of Findings:

Stephen L. Johnson,
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 2/24/86

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Registration Standard for Oryzalin

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) decision to classify Oryzalin as a class C (possible human) carcinogen. The review was conducted in an open meeting held in Arlington, Virginia, on February 11, 1986. All Panel members were present for the review. In addition, Dr. David Gaylor, Director of the Biometry Staff at the National Center for Toxicological Research, served as an ad hoc member of the Panel.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

General Comments on Carcinogen Classification

The Panel concurs that it is necessary to categorize chemicals as to their apparent carcinogenic risk to man. The Panel is concerned that the categories outlined in the Agency's Cancer Guidelines are somewhat limited in scope. For only a small number of specific chemicals is there epidemiologic evidence of their carcinogenicity in man, either sufficient evidence (Group A) or limited evidence (Group B-1). Thus, most chemicals that are carcinogenic for animals have been placed in Groups B-2 and C. Category D has apparently not been used. The Panel urges the Agency to attempt to develop a more discriminatory classification scheme.

Oryzalin

The Agency requested the Panel to focus its attention upon a set of issues relating to the pesticide Oryzalin. There follows a list of the issues and the SAP's response to the issues.

1. Based on the weight of evidence assessment with emphasis on the rat feeding study the Agency has classified Oryzalin as a class C (possible human) carcinogen. The Agency specifically requests any comments that the Panel may wish to present with regard to its assessment of the weight of evidence and subsequent determination of carcinogenicity according to the Agency's Cancer Guidelines.

Panel Response:

The position taken by the Agency was succinctly stated in their "scientific issues" document and in a well organized oral presentation. The reason for choosing classification C is a list of convincing arguments for not going into Category B. The most important of these are: (1) oryzalin did not produce tumors in multiple species, (2) the tumors produced in the thyroid of the rat are possibly secondary to the antithyroid action of the compound, (3) the increased incidence of skin and mammary tumors in the exposed animals was restricted to benign tumors, and (4) the compound is not mutagenic in a long series of short-term assays. The SAP concludes that the carcinogenic data are compatible with Category C.

The SAP urges that the EPA should delete from their documents the statement that benign and malignant tumors of the skin and mammary glands are increased. Only benign tumors were increased in these tissues.

The SAP noted that a number of compounds having antithyroid action tended to produce skin tumors. The question arose that there might be a connection between the two effects.

FOR THE CHAIRMAN

Certified as an accurate report of Findings:

Stephen L. Johnson,
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 2/24/86

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Registration Standard for Amitraz

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) decision to classify Amitraz as a class C (possible human) carcinogen. The review was conducted in an open meeting held in Arlington, Virginia, on February 12, 1986. All Panel members, except Dr. James A. Swenberg, were present for the review. In addition, Dr. David Gaylor, Director of the Biometry Staff at the National Center for Toxicological Research, served as an ad hoc member of the Panel.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency and from Ms. Paula Paul of NOR-AM Chemical Company and Dr. Tom Kakuk of the Upjohn Company.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

General Comments on Carcinogen Classification

The Panel concurs that it is necessary to categorize chemicals as to their apparent carcinogenic risk to man. The Panel is concerned that the categories outlined in the Agency's Cancer Guidelines are somewhat limited in scope. For only a small number of specific chemicals is there epidemiologic evidence of their carcinogenicity in man, either sufficient evidence (Group A) or limited evidence (Group B-1). Thus, most chemicals that are carcinogenic for animals have been placed in Groups B-2 and C. Category D has apparently not been used. The Panel urges the Agency to attempt to develop a more discriminatory classification scheme.

Amitraz

The Agency requested the Panel to focus its attention upon a set of issues relating to the pesticide Amitraz. There follows a statement of the issue and the SAP's response to the issue.

1. Based on our weight of the evidence assessment with emphasis on the second mouse study, the Agency has classified Amitraz as a class C (possible human) carcinogen. The Agency specifically requests any comment that the Panel may wish to present with regard to its assessment of the weight of evidence and subsequent determination of carcinogenicity according to the Agency's Cancer Guidelines.

Panel Response:

Both the Agency and the company agree that Amitraz at the high dose level (400 ppm) produced a statistically significant increase in liver tumors, both benign and malignant in female mice. The company contended that at 400 ppm the female mice were compromised physiologically and this dose was far in excess of the MTD. Within the Guidelines it would be possible to classify this compound in either class C or D with respect to the liver tumors. Data were presented supporting an indirect hormonal mechanism for tumorigenesis which may not be operative at lower doses. The Panel believes that the weight of evidence is inadequate to clearly categorize the carcinogenicity of Amitraz. Amitraz was also found to be negative in a battery of genotoxicity tests. It is for these reasons that the Panel recommends that Amitraz be classified in Class D. The committee also recommends that the Agency further consider data which the company may possess or wish to obtain which would resolve the current uncertainties.

FOR THE CHAIRMAN

Certified as an accurate report of Findings:

Stephen L. Johnson,
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 2/24/86

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Registration Standard for Acephate

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) decision to classify Acephate as a class C (possible human) carcinogen. The review was conducted in an open meeting held in Arlington, Virginia, on February 12, 1986. All Panel members were present for the review.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency and from Dr. Nancy Rachman and Dr. Ward Richter of Chevron Chemical Company.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

General Comments on Carcinogen Classification

The Panel concurs that it is necessary to categorize chemicals as to their apparent carcinogenic risk to man. The Panel is concerned that the categories outlined in the Agency's Cancer Guidelines are somewhat limited in scope. For only a small number of specific chemicals is there epidemiologic evidence of their carcinogenicity in man, either sufficient evidence (Group A) or limited evidence (Group B-1). Thus, most chemicals that are carcinogenic for animals have been placed in Groups B-2 and C. Category D has apparently not been used. The Panel urges the Agency to attempt to develop a more discriminatory classification scheme.

Acephate

The Agency requested the Panel to focus its attention upon a set of issues relating to the pesticide Acephate. There follows a statement of the issue and the SAP's response to the issue.

1. Based on the weight of the evidence assessment, with emphasis on the mouse study, the Agency has classified Acephate as a class C (possible human) carcinogen. The Agency specifically requests any comments that the Panel may wish to present with regard to its assessment of the weight of the evidence and subsequent determination of carcinogenicity according to the Agency's Cancer Guidelines.

Panel Response:

The Panel reviewed the weight of evidence for the carcinogenic potential of Acephate. Acephate has been demonstrated to be a weak genotoxicant in a number of in vitro studies, but was negative in several in vivo investigations. The chemical caused a significant increase in liver tumors only in female mice exposed to 1,000 ppm acephate. This dose appeared to exceed the MTD with respect to body weight, but not survival. The Panel believes that Acephate could be categorized in either Group C or D. The presence of positive genotoxic data was considered pivotal in placing acephate in Group C. Additional data may further clarify the appropriateness of this decision.

FOR THE CHAIRMAN'

Certified as an accurate report of Findings:

Stephen L. Johnson,
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 2/24/86

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with Subdivision U of the Pesticide Assessment Guidelines

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the proposed Pesticide Assessment Guidelines, Subdivision U. The review was conducted in an open meeting held in Arlington, Virginia, on February 12, 1986. All Panel members were present for the review.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency and from Richard Kuarr representing the National Agricultural Chemicals Association, and Dr. Douglas Baugher, Orius Associates, Inc..

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

Subdivision U

The Agency specifically requests the Panel's consideration in regard to the following areas discussed in the guidelines:

1. The Agency recommends the routine use of passive dosimetry techniques to estimate exposure, but will use the results of biological monitoring for pesticides whose pharmacokinetics are well understood and when a carefully designed protocol has been approved by the Agency.

Panel Response:

Dosimetry results are not directly related to the toxicity hazard to exposed persons. EPA should encourage the concurrent use of both dosimetry and biological monitoring methods to the greatest extent possible, rather than considering them alternatives.

2. Since a large fraction of total dermal exposure is typically exposure to the hands, estimating hand exposure is very important. The Agency recommends either the hand rinse method or using lightweight monitoring gloves.

Panel Response:

The SAP agrees. However, certain chemicals may require special consideration because of rapid absorption, persistence in skin, re-excretion, etc..

3. The criteria for when field monitoring studies must be carried out are:

   a. There is acute or chronic toxicological concern for a pesticide product.

   b. The Agency does not have sufficient exposure data available to adequately estimate the level of exposure.

   Both criteria must be met before a study is required.

Panel Response:

The Panel believes this is a reasonable approach.

4. The Agency requires 9 replicates for studies measuring exposure of aircraft pilots and 15 replicates for those monitoring all other tasks. These somewhat arbitrary figures are based on the scientific advantages of large sample sizes balanced with the costs and practicality of conducting exposure studies. The number of replicates required for pilots is lower because, under certain conditions, time constraints and/or the limited number of appropriate subjects would place an undue burden on the registrants were a larger sample size required.

Panel Response:

The Panel agrees with EPA's intention of finding the best possible compromise between the desire for large sample sizes on the one hand, and the high cost of exposure studies on the other hand. However, the numerical requirements for replicates in this section appear to be too rigid. The number of replicates should be based upon the tightness of the data from similar studies.

5. In many application scenarios, it has been shown that the physical parameters of application (application method, type of formulation, application rate, etc.) and not the chemical properties of the pesticide are most important in determining the level of exposure. The Agency is therefore actively pursuing the

establishment of "generic" data bases for various application methods. These data bases are comprised of the results of exposure monitoring studies for different pesticides applied under similar conditions. These data bases, when sufficiently developed, are then used to estimate worker exposure for other pesticides applied under like conditions, thus eliminating the need for exposure studies for every pesticide/site/application method combination.

Panel Response:

The Panel agrees with EPA's intention to develop a generic data base of exposure studies. However, the Panel feels that chemical properties of the active ingredient may well affect bioavailability results and should therefore also be given due consideration.

6. When pesticides are used at indoor sites, frequently the person who applies the product (or other people) works or resides at the indoor site. The Agency is requiring that for indoor applications, post application monitoring of potential dermal and inhalation exposure be carried out using the same passive dosimetry techniques as for outdoor sites. Post application monitoring must be carried out so the decline in potential exposure as a function of time can be defined.

Panel Response:

The SAP feels that the guidelines for indoor monitoring are not as well thought out as those for outdoor uses. The Panel feels this section of Subdivision U requires further work before finalization.

FOR THE CHAIRMAN

Certified as an accurate report of Findings:

Stephen L. Johnson,
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 2/24/86

University of Cincinnati
Medical Center

Institute of Environmental ...

Kettering Laboratory (ML 56)
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

OCT 1 1986

October, 25, 1986

Timothy J. Long, Ph.D.
Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167

Subject: Roundup(R)
Chronic Mouse Study

Dear Dr. Long,

I have reviewed the arguments for and against repeating the mouse study. I agree with your conclusion that it has no merit to initiate an additional experiment. The reasons are the following.

1. As I pointed out in my evaluation of 10-17-85, the CD-1 mouse has a high background incidence of neoplasms in different organs. The historical data on kidney tumors in this strain showed a relative large variation in their spontaneous incidence. I am certain that a repeat study would not lead to more meaningful data.

2. Because of the high incidence of spontaneous neoplasms in this mouse, one should give strong consideration to the following:

a. There are large numbers of initiated cells in many of the organs (expression of true carcinogenicity of whatever initiated these cells).

b. The toxic effect of any chemical could cause activation of these initiated cells and also promote tumor growth. This could occur in the primary target organ of the toxicant or in secondary organs. Roundup did not show any

renal toxicity, therefore, no activation or promotion could have taken place. No significant tumor development was present related to the dose of the material, and by comparison to historical data.

3. The genotoxic tests of the material were negative. This supports strongly the argument that Roundup is not an initiator (carcinogen).

In my opinion the above arguments strongly deny a repeat study with the CD-1 mouse. To satisfy the requirements of the agency a rat study is indicated.

Sincerely yours,

Klaus L. Stemmer, M.D.

Glyphosate Mouse Oncogenicity Study (BD-77-420)

Monsanto believes that it is not necessary to repeat the glyphosate mouse oncogenicity study (BD-77-420). If one applies the decision tier scheme for determining the need to repeat oncogenicity studies as discussed in the EPA position paper on maximum tolerated dose (MTD)[1], it is apparent that none of the criteria necessitating a repeat study have been met. Outlined below is a level by level discussion of each of these criteria and the reasons why none have been met for the study in question.

Level 1 - Nearness to the Apparent MTD

"If the highest dose tested (HDT) is greater than or equal to one-half the apparent MTD, as judged from subchronic data or other chronic studies, no retesting is required."

Monsanto Response: The HDT in the glyphosate mouse oncogenicity study (30,000 ppm in the diet) was selected based upon the results of a 90-day subchronic mouse feeding study conducted at dietary concentrations of 5,000, 10,000, and 50,000 ppm. Evidence of subchronic toxicity, as evidenced by reduced body weight gain, was observed at 50,000 ppm. Body weight gains were reduced 24% and 18% for males and females, respectively. No effect upon body weight gain was observed at 5,000 or 10,000 ppm. It was felt that 50,000 ppm would be too high for a lifetime study. Body weight effects due to prolonged exposure at such a high level would probably be life threatening. Therefore, the HDT was chosen at 30,000 ppm. Since this concentration is greater than one-half the apparent MTD in the 90-day study (50,000 ppm), the first criteria necessitating a repeat study has not been met.

Furthermore, the HDT exceeds by greater than four-fold the dosage of 1 gram/kg/day (7,000 ppm for mice) which the Agency states[1] as an adequate upper limit for assessing human risks from animal oncogenicity studies with pesticides.

Level 2 - Demonstrated Oncogenicity

"If the test substance is demonstrated to be an oncogen in another species, retesting is required."

Monsanto Response: Glyphosate was not oncogenic in a 26-month rat feeding study (BD-77-416). This study had previously been accepted by the Agency as a valid study demonstrating lack of oncogenic potential. However, the Agency has expressed the concern that a MTD may not have been demonstrated in this study. Monsanto has agreed to repeat the rat oncogenicity study. Therefore, unless the repeat rat study were to demonstrate oncogenic potential, there is currently no justification for a repeat mouse study based upon the criteria at Level 2.

Level 3 - Genotoxicity
"If no genotoxicity is demonstrated in an acceptable battery of tests including one study each to detect effects at the gene, chromosome, and DNA level, consideration at the next level is required."

Monsanto Response: The results of an extensive battery of genotoxicity assays designed to assess each of these endpoints have uniformly been negative. Therefore, the criteria for retesting at this level have not been met, and consideration at level 4 is required.

Level 4 - Oncogenicity of Structural Analogs
"If structural analogs of the test substance or known metabolites have been shown to be oncogenic in animals or man, retesting is required."

Monsanto Response: Neither glyphosate nor any of its known metabolites are structurally related to any known oncogen. Thus, the criteria for retesting at this level have not been met.

Level 5 - Absolute Value of HDT
"If the HDT is 0.5 gm/kg b.w./day, no retesting is required."

Monsanto Response: The HDT in the lifetime mouse study was much greater than 0.5 gm/kg/day. For male mice, the time-weighted average daily exposure at the HDT was 4.84 gm/kg/day. The corresponding figure for female mice at the HDT was 5.87 gm/kg/day. According to this criteria, therefore, retesting is not required.

Level 6 - HDT Relative to Dose Tested in Second Species of an Oncogenicity Study with an MTD
"If the HDT in the study under evaluation expressed in mg/kg/day, is at least equal to the HDT in mg/kg/day in an acceptable oncogenicity study in another species, then no retesting is required. If, however, the HDT is less than ..., consideration at the next level (level 7) is required."

Monsanto Response: As discussed in Level 2, another oncogenicity study has been conducted with glyphosate in rats (BD-77-416). In that study, the HDT was 31 and 34 mg/kg/day for male and female rats, respectively. The HDT in the mouse study was 150-170 times greater than that in the rat study. Furthermore, the maximum dosage level that would be tested in the planned repeat rat study is 20,000 ppm. The HDT in the mouse study exceeds this dosage level (1000 mg/kg) by greater than four-fold. Therefore, consideration at level 7 is required.

Level 7 - Margin of Safety (MOS) Calculated for HDT vs Human Exposure
"If the MOS (ratio) between the HDT and the highest expected level of human exposure is greater than or equal to 1000, no retesting is required."

Monsanto Response: If one uses the Theoretical Maximum Residue Contribution (TMRC) based upon existing tolerances (1.4238 mg/day) as an upper bound on expected human exposure, then there is at least a 200,000 fold MOS* between the HDT in the mouse study and expected human exposure. Therefore, according to the criteria at this level, no retesting is required.

*HDT = 4840-5870 mg/kg/day
TMRC = 1.4238 mg/day
Thus: (4840 mg/kg/day)(60 kg man) ÷ 1.4238 mg/day = 203,961

References

[1]Harris, J.E., Farber, T.M., Engler, R., Quest, J.A., and Skinner, C.S.; Position Paper on Maximum Tolerated Dose (MTD) In Oncogenicity Studies - DRAFT. April, 1986.

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE, VIENNA, VIRGINIA 22180, U.S.A.

REPRESENTATIVE HISTORICAL CONTROL DATA

PART I:	RODENT LONGEVITY
PART II:	NEOPLASIA IN SPRAGUE-DAWLEY RATS
PART III:	NEOPLASIA IN UNTREATED B6C3F1 MICE
PART IV:	NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CORN OIL IN THE DIET
PART V:	NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CORN OIL ADMINISTERED BY GAVAGE
PART VI:	NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CARBOXYMETHYL-CELLULOSE ADMINISTERED BY GAVAGE
PART VII:	NEOPLASIA IN UNTREATED CD-1® MICE
PART VIII:	NEOPLASIA IN UNTREATED CD-1® F1 MICE
PART IX:	NEOPLASIA IN CD-1® CONTROL MICE TREATED WITH DISTILLED WATER ADMINISTERED BY GAVAGE
PART X:	NEOPLASIA IN CD-1® CONTROL MICE TREATED WITH 0.5% TRAGACANTH IN DISTILLED WATER ADMINISTERED BY GAVAGE
PART XI:	HEMATOLOGY REFERENCE RANGES
PART XII:	CLINICAL CHEMISTRY REFERENCE RANGES

NOTE: Historical control data generated in-house at Hazleton Laboratories America, Inc.

updated 7/1/83

REPRESENTATIVE HISTORICAL CONTROL DATA

PART VII

NEOPLASIA IN UNTREATED CD-1® MICE

HAZLETON LABORATORIES AMERICA, INC.
SUMMARY OF NEOPLASIA IN UNTREATED CONTROL CD-1® MICE

THE FINDINGS PRESENTED IN THIS SUMMARY ARE FROM UNTREATED CONTROL MICE SACRIFICED AFTER 91 TO 105 WEEKS.

THE TERM 'POSITIVE TOTALS' REPRESENTS THE TOTAL NUMBER OF POSITIVE FINDINGS FROM STUDIES WHERE THERE WERE ONE OR MORE OCCURRENCES OF THE INDICATED NEOPLASM IN EACH SEX. THE DATA FROM THESE STUDIES, INCLUDING THE NUMBER OF TISSUES EXAMINED, ARE PRESENTED.

THE TERM 'OVERALL TOTALS' REPEATS THE TOTAL NUMBER OF POSITIVE FINDINGS AND ALSO PRESENTS THE TOTAL NUMBER OF TISSUES OBSERVED FROM ALL QUALIFYING STUDIES, THAT IS, THOSE STUDIES WITH POSITIVE AS WELL AS NEGATIVE FINDINGS.

WHEN POSITIVE FINDINGS ARE LISTED FOR TISSUE MASS, OTHER LESIONS, MULTIPLE ORGANS, OR OTHER NON-PROTOCOL TISSUES, THE TOTAL NUMBER OF TISSUES EXAMINED REPRESENTS THE TOTAL NUMBER OF ANIMALS EXAMINED AT THAT INTERVAL OR THE TOTAL NUMBER OF ANIMALS ON STUDY, AS APPROPRIATE.

'OVERALL PERCENT' IS THEN CALCULATED USING THE 'OVERALL TOTALS' FIGURE.

THE COMPUTER ESTABLISHES 'RANGE OF PERCENTAGES' FROM THE DATA COMPRISING 'POSITIVE TOTALS'.

NEOPLASIA IN CD-1® MICE-UNTREATED CONTROLS

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES
*** TISSUE NAME--KIDNEY ***				
CARCINOMA				
	1	10	0	10
POSITIVE TOTALS--	1	10	0	10
OVERALL TOTALS---	1	284	0	294
OVERALL PERCENT--	0.4		0.0	
RANGE OF PERCENTAGES--	10 -- 10		0 -- 0	
*** TISSUE NAME--LIP ***				
PAPILLOMA				
	0	10	1	10
POSITIVE TOTALS--	0	10	1	10
OVERALL TOTALS---	0	10	1	10
OVERALL PERCENT--	0.0		10.0	
RANGE OF PERCENTAGES--	0 -- 0		10 -- 10	

REPRESENTATIVE HISTORICAL CONTROL DATA

PART VIII

NEOPLASIA IN UNTREATED CD-1® F1 MICE

HAZLETON LABORATORIES AMERICA, INC.
SUMMARY OF NEOPLASIA IN UNTREATED CONTROL CD-1® F1 MICE

THE FINDINGS PRESENTED IN THIS SUMMARY ARE FROM UNTREATED F1 GENERATION CONTROL MICE SACRIFICED AFTER 91 TO 105 WEEKS.

THE TERM 'POSITIVE TOTALS' REPRESENTS THE TOTAL NUMBER OF POSITIVE FINDINGS FROM STUDIES WHERE THERE WERE ONE OR MORE OCCURRENCES OF THE INDICATED NEOPLASM IN EACH SEX. THE DATA FROM THESE STUDIES, INCLUDING THE NUMBER OF TISSUES EXAMINED, ARE PRESENTED.

THE TERM 'OVERALL TOTALS' REPEATS THE TOTAL NUMBER OF POSITIVE FINDINGS AND ALSO PRESENTS THE TOTAL NUMBER OF TISSUES OBSERVED FROM ALL QUALIFYING STUDIES, THAT IS, THOSE STUDIES WITH POSITIVE AS WELL AS NEGATIVE FINDINGS.

WHEN POSITIVE FINDINGS ARE LISTED FOR TISSUE MASS, OTHER LESIONS, MULTIPLE ORGANS, OR OTHER NON-PROTOCOL TISSUES, THE TOTAL NUMBER OF TISSUES EXAMINED REPRESENTS THE TOTAL NUMBER OF ANIMALS EXAMINED AT THAT INTERVAL OR THE TOTAL NUMBER OF ANIMALS ON STUDY, AS APPROPRIATE.

WHERE INDIVIDUAL STUDY DATA ARE FOLLOWED BY THE SUPER-SCRIPT 'A', THE NUMBER PRESENTED REPRESENTS THE NUMBER OF ANIMALS SACRIFICED AT TERMINATION RATHER THAN THE NUMBER OF TISSUES EXAMINED.

'OVERALL PERCENT' IS THEN CALCULATED USING THE 'OVERALL TOTALS' FIGURE.

THE COMPUTER ESTABLISHES 'RANGE OF PERCENTAGES' FROM THE DATA COMPRISING 'POSITIVE TOTALS'.

NEOPLASIA IN CD-1® F1 MICE-UNTREATED CONTROLS

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES)
*** TISSUE NAME--KIDNEY ***				
TUBULAR CELL ADENOMA				
	1	15	0	15
	1	14	0	26
POSITIVE TOTALS--	2	29	0	41
OVERALL TOTALS---	2	56	0	81
OVERALL PERCENT--	3.6		0.0	
RANGE OF PERCENTAGES--	7 --	7	0 --	0
TUBULAR CELL CARCINOMA				
	1	15	0	15
POSITIVE TOTALS--	1	15	0	15
OVERALL TOTALS---	1	56	0	81
OVERALL PERCENT--	1.8		0.0	
RANGE OF PERCENTAGES--	7 --	7	0 --	0
*** TISSUE NAME--LIVER ***				
HEMANGIOSARCOMA				
	0	15	2	15
POSITIVE TOTALS--	0	15	2	15
OVERALL TOTALS---	0	75	2	100
OVERALL PERCENT--	0.0		2.0	
RANGE OF PERCENTAGES--	0 --	0	13 --	13

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 24 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Transmittal of the Final FIFRA Scientific Advisory Panel Reports on the February 11-12, 1986 Meeting

TO: Steven Schatzow, Director
Office of Pesticide Programs (TS-766)

The above mentioned meeting of the FIFRA Scientific Advisory Panel (SAP) was an open meeting held in Arlington, Virginia to review the following topics:

(1) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Glyphosate;

(2) A set of scientific issues in connection with the Agency's proposed action on the non-wood uses of Pentachlorophenol as set forth in the Position Document 4;

(3) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Oryzalin;

(4) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Amitraz;

(5) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Acephate;

(6) A set of scientific issues being considered by the Agency in connection with Subdivision U of the Pesticide Assessment Guidelines.

Please find attached the SAP's final reports on the six issues discussed at the meeting.

Stephen L. Johnson, Executive Secretary
FIFRA Scientific Advisory Panel (TS-769)

Attachments

cc: Panel Members
John A. Moore
James Lamb
Al Heier
Susan Sherman
John Melone
Douglas Campt
EPA Participants

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Registration Standard for Glyphosate

---

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) decision to classify Glyphosate as a class C (possible human) carcinogen. The review was conducted in an open meeting held in Arlington, Virginia, on February 11, 1986. All Panel members, except Dr. Thomas W. Clarkson, were present for the review. In addition, Dr. David Gaylor, Director of the Biometry Staff at the National Center for Toxicological Research, served as an ad hoc member of the Panel.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency and from Mr. Robert Harness and Dr. Timothy Long of Monsanto Company.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

General Comments on Carcinogen Classification

The Panel concurs that it is necessary to categorize chemicals as to their apparent carcinogenic risk to man. The Panel is concerned that the categories outlined in the Agency's Cancer Guidelines are somewhat limited in scope. For only a small number of specific chemicals is there epidemiologic evidence of their carcinogenicity in man, either sufficient evidence (Group A) or limited evidence (Group B-1). Thus, most chemicals that are carcinogenic for animals have been placed in Groups B-2 and C. Category D has apparently not been used. The Panel urges the Agency to attempt to develop a more discriminatory classification scheme.

Glyphosate

The Agency requested the Panel to focus its attention upon a set of issues relating to the pesticide Glyphosate. There follows a list of the issues and the SAP's response to each question.

1. Based on the Agency's weight of the evidence assessment with emphasis on the mouse kidney tumors, the Agency has classified Glyphosate as a class C (possible human) carcinogen. The Agency specifically requests any comment that the Panel may wish to present with regard to its assessment of the weight of evidence and subsequent determination of carcinogenicity according to the Agency's Cancer Guidelines.

2. The Agency requests also that the Panel consider what weight should be given to this marginal increase in kidney tumors, the importance of this type of tumor in the assessment of the carcinogenicity of Glyphosate, and the weight placed on historical and concurrent controls for this type of evaluation.

Panel Response:

In the instance of Glyphosate, the Panel concurs that the data on renal tumors in male mice are equivocal. Only small numbers of tumors were found in any group, including those at the highest dose which appear to have exceeded the maximal tolerated dose. The vast majority of the pathologists, who examined the proliferative lesion in the male control animal, agreed that the lesion represented a renal adenoma. Therefore, statistical analysis of the data should utilize this datum. In addition, the statistical analysis shall be age-adjusted; when this is done, no oncogenic effect of Glyphosate is demonstrated using concurrent controls. Nevertheless, the occurrence of three neoplasms in high dose male mice is unusual and using historical controls is statistically highly significant. Furthermore, categorization of the oncogenic risk of Glyphosate is complicated by the fact that doses used in the rat study do not appear to have reached the maximal tolerated dose. Under these circumstances, the Panel does not believe that it is possible to categorize Glyphosate clearly into Group C (possible human carcinogen) or Group E (no evidence of carcinogenicity for humans). The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions.

Regarding the issue of using historical or concurrent controls, the Panel believes that this has to be decided on a case-by-case basis. For Glyphosate, the historical control data support that there may be reason for concern. However, the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls.